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# Contralateral Hemispheric Cerebral Blood Flow Measured with Arterial Spin Labeling Can Predict Outcome in Acute Stroke

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## ***Abstract***

**Background and Purpose:** Imaging is frequently used to select acute stroke patients for intra-arterial treatment (IAT). Quantitative cerebral blood flow (CBF) can be measured non-invasively with arterial spin labeling (ASL) magnetic resonance imaging (MRI). CBF levels in the contralateral (unaffected) hemisphere may affect capacity for collateral flow and patient outcome. The goal of this study was to determine whether higher contralateral CBF (cCBF) in acute stroke identifies patients with better 90-day functional outcome.

**Methods:** Patients were part of the prospective, multicenter ‘Imaging Collaterals in Acute Stroke’ (iCAS) study between 2013 and 2017. Consecutive patients were enrolled after being diagnosed with anterior circulation acute ischemic stroke. Inclusion criteria were ischemic anterior circulation stroke, baseline National Institutes of Health Stroke Scale (NIHSS)  $\geq 1$ , pre-stroke modified Rankin Score (mRS)  $\leq 2$ , onset-to-imaging-time (OIT)  $< 24$  hrs, with imaging including diffusion-weighted imaging (DWI) and ASL. Patients were dichotomized into high and low cCBF groups based on median cCBF. Outcomes were assessed by day 1 and 5 NIHSS; and day 30 and 90 mRS. Multivariable logistic regression was used to test whether cCBF predicted good neurological outcome (mRS 0-2) at 90 days.

**Results:** Seventy-seven patients (41 female) met the inclusion criteria with median (inter-quartile range) age 66 (55-76) yrs, OIT 4.8 (3.6-7.7) hrs, and baseline NIHSS 13 (9-20). Median cCBF was 38.9 (31.2-44.5) ml/100g/min. Higher cCBF predicted good outcome at day 90 (OR 4.6, 95% CI 1.4-14.7,  $p=0.01$ ), after controlling for baseline NIHSS, DWI lesion volume, and intra-arterial treatment.

**Conclusion:** Higher quantitative contralateral CBF at baseline is a significant predictor of good neurological outcome at day 90. cCBF levels may inform decisions regarding stroke triage, treatment of acute stroke, and general outcome prognosis.

**Clinical Trial Registration:**

Imaging Collaterals in Acute Stroke (iCAS), unique identifier: NCT02225730, clinical trial registration URL: <https://clinicaltrials.gov/ct2/show/NCT02225730>

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## Introduction

Following an acute vessel occlusion, perfusion of the ischemic penumbra is sustained by collateral flow. Evaluation of cerebral hemodynamics in the stroke-affected, ipsilateral hemisphere to identify appropriate patients for intra-arterial thrombectomy (IAT) is a common practice.<sup>1-4</sup> To the best of our knowledge, no studies have investigated the predictive role of quantitative perfusion biomarkers in the contralateral, unaffected hemisphere. Higher cerebral blood flow (CBF) in the contralateral hemisphere might be associated with a greater capacity to mobilize collateral flow to affected regions in the ipsilateral hemisphere or be a marker for better cardiac output, and thereby be associated with better neurological outcomes.

Arterial spin labeling (ASL) MRI enables measurement of quantitative CBF without the need for contrast agents and can be acquired in the acute stroke setting.<sup>5</sup> ASL differs from the more commonly-applied contrast-enhanced methods with MRI or CT perfusion-weighted imaging (PWI), which do not routinely provide quantitative CBF information, instead providing relative measurements. Meanwhile, ASL is prone to underestimate CBF in ischemic regions due to prolonged arterial arrival times.<sup>6-8</sup> However, these issues are less prevalent in the contralateral hemisphere, where there is usually no acute ischemic event or large vessel occlusion. In this study, we hypothesized that the high contralateral CBF (cCBF) at the time of ischemic stroke is associated with better outcome.

## **Materials and Methods**

### **Study Design and Patient Selection**

The cohort is part of the ongoing observational, prospective, multi-center ‘Imaging Collaterals in Acute Stroke’ (iCAS) study (unique identifier: NCT02225730, clinical trial registration URL: <https://clinicaltrials.gov/ct2/show/NCT02225730>). The iCAS study has been approved by the Institutional Review Board. Informed consent was obtained from all subjects. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients were enrolled between November 2013 and August 2017, after being diagnosed with an acute ischemic stroke at four participating sites: Stanford University (Stanford, CA, United States), University of Pittsburgh Medical Center (UPMC, Pittsburgh, PA, United States), Swedish Medical Center (Seattle, WA, United States), and Eden Medical Center (Castro Valley, CA, United States). Patients imaged <24 hrs from last seen well and who were considered for intra-arterial endovascular therapy of an anterior circulation occlusion were eligible. Specific inclusion criteria for patients were (a) anterior circulation ischemic hemispheric stroke, (b) baseline National Institutes of Health Stroke Scale (NIHSS)  $\geq 1$ , (c) <24 hrs onset-to-imaging-time (OIT), (d) pre-stroke mRS  $\leq 2$ , (e) age  $\geq 18$  yrs, (f) technically adequate imaging including diffusion-weighted imaging (DWI) and ASL. Exclusion criteria were (a) MRI contraindications and (b) pregnancy. If deemed appropriate by the treating clinicians, patients received intra-arterial therapy (IAT).

### **Imaging Acquisition and Analysis**

Imaging was performed at either 1.5T (Signa, GE Healthcare, Milwaukee, WI, USA) or 3T (750w, GE Healthcare, Milwaukee, WI, USA). ASL scans included single-delay pseudocontinuous ASL<sub>9</sub>

with labeling duration (LD) = 1.45s, post-labeling delay (PLD) = 2.025s (at 1.5T); and a multi-delay (5-delay) ASL with LD = 2s, PLD = 0.7, 1.275, 1.85, 2.425, and 3s (at 3.0T). Proton density (PD)-weighted images were collected for quantification. The ASL images were reconstructed with an interpolated resolution of  $1.9 \times 1.9 \times 6 \text{ mm}^3$  (1.5T) or  $1.9 \times 1.9 \times 4 \text{ mm}^3$  (3.0T). Isotropic DWI images were acquired with TR/TE 4000/77.5ms,  $b=1000 \text{ s/mm}^2$  and spatial resolution of  $0.9 \times 0.9 \times 5 \text{ mm}^3$ . Infarct volume was calculated using RAPID software (version 4.5.1, iSchemaView, Menlo Park, CA, USA).

For single-delay ASL, the CBF maps were quantified using the simplified equation from Alsop et al.<sup>5</sup> For multi-delay ASL, arterial transit time (ATT) corrected CBF maps were generated from a kinetic signal model<sup>10</sup> with assumed arterial and tissue  $T_1$  of 1.65s and 1.5s, respectively. This was performed using an automated standardized script in MATLAB R2013b (version 8.2.0.701, The MathWorks, Inc., Natick, MA, USA) using SPM8 (Statistical Parametric Mapping, The Wellcome Trust Centre for Neuroimaging, University College London, UK).

All perfusion and diffusion images were first registered to the  $T_1$ -weighted structural scans and then registered and normalized to the Montreal Neurological Institute (MNI) template. The atlas' standard gray matter mask was then applied. CBF values were extracted automatically in gray matter regions-of-interest at four supratentorial levels corresponding to those assessed as part of the Alberta Stroke Program Early CT Score (ASPECTS) system (Supplemental Figure I, please see <http://stroke.ahajournals.org>). Mean contralateral CBF (cCBF) was calculated across all ROIs in the unaffected brain hemisphere. Additional analyses based on follow-up imaging and corresponding imaging outcome measures are reported in the Supplemental Material (Supplemental Methods, please see <http://stroke.ahajournals.org>).

## **Clinical Assessment**

Neurological outcome was assessed by using NIHSS and the modified Rankin Score (mRS) at several timepoints. NIHSS was measured at baseline before any intervention (NIHSS baseline), at 24 hrs (NIHSS day 1), and at day 5 or at discharge (NIHSS day 5). mRS was assessed at day 30 (mRS day 30) and day 90 (mRS day 90) either by telephone or clinical visit. The primary endpoint was good neurological outcome at day 90, defined as mRS day 90  $\leq 2$ . Secondary analyses were performed for NIHSS day 1, day 5, and mRS day 30. Any missing values for NIHSS and mRS were imputed with data from last available visit using the traditional last observation carried forward (LOCF) method as described in the approved iCAS study protocol. For deceased patients, worst-case values were assigned to all time points after death: NIHSS=42, mRS=6. We tracked the etiological subtype of acute ischemic stroke using the TOAST classification (Supplemental Table I, please see <http://stroke.ahajournals.org>).<sup>11</sup>

## **Regression Model and Statistical Analysis**

The full cohort was divided into patients with cCBF above the median ('high cCBF group') and below the median ('low cCBF group'). An adjusted multivariable logistic regression model was applied to investigate the relationship between cCBF group and good 90-day outcome. We controlled for the following factors, which were analyzed in a univariable analysis as potentially being relevant: baseline NIHSS, DWI lesion volume, and the use of IAT after imaging.

Statistical analyses were performed using Stata version 15.1 (StataCorp LP, College Station, TX, USA). Results are reported as medians with interquartile ranges (IQR). Outcome differences were assessed with Mann-Whitney U (NIHSS) and Fisher's exact test (mRS). All analyses were 2-sided;



level of significance was set to  $\alpha < 0.05$ . Regression results are presented for each variable including odds ratio (OR), p-value, and 95% confidence interval (95% CI).

## Results

### Patient Population

109 patients underwent MRI. Of these, 32 were excluded for the following reasons: poor image quality and/or motion artifacts (n=19), no ASL performed at baseline (n=7), pre-stroke mRS  $\geq 3$  (n=3), OIT  $>24$ hrs (n=1), baseline NIHSS=0 (n=1), and bilateral stroke (n=1). Seventy-seven (77) patients were included in the analysis (Table 1): 41 (53%) females, age 66 (55-76) yrs, OIT 4.8 (3.6-7.7) hrs, baseline NIHSS 13 (9-20). Sixty-nine (90%) were scanned at 3T and the rest at 1.5T. A total of 46 patients (60%) received tissue plasminogen activator (tPA) before the baseline MRI scan. Following the baseline MRI, 41 patients underwent IAT (53%); in 33/41 (80%) of those, the final Thrombolysis in Cerebral Infarction (TICI) score was 2b or 3. When comparing cCBF values for single-delay (37.6 ml/100g/min, IQR 30.2-43.6) vs. multi-delay ASL (39.0 ml/100g/min, IQR 31.8-44.5), there was no significant difference found ( $p=0.87$ ). There was also no difference in the fraction of patients in the high and low cCBF groups regarding ASL type (Supplemental Table II, please see <http://stroke.ahajournals.org>).

### Dichotomized cCBF

There were no significant differences in the clinical baseline characteristics between high and low cCBF groups (Table 1). In particular, there was no significant linear correlation between DWI lesion size and cCBF (Supplemental Figure II, please see <http://stroke.ahajournals.org>). Median NIHSS at baseline/day 1/day 5 for low and high cCBF groups was 13/14/11 and 13/6.5/4.5, respectively (Figure 1). While there was no significant difference at baseline, NIHSS was significantly different between groups on both day 1 ( $p=0.016$ ) and day 5 ( $p=0.003$ ). High cCBF

significantly predicted good clinical outcomes as assessed by mRS at day 90 ( $p=0.011$ ) (Figure 2), with 55% of high cCBF patients in the mRS 0-2 group compared with only 26% for the low cCBF group. There was also a trend towards better outcome at day 30, but this was not statistically significant.

### **Multivariable analysis**

The univariate analysis identified the variables high cCBF, baseline NIHSS, DWI lesion volume, and intra-arterial treatment as significant factors for outcome prediction. In the multivariable analysis, patients were roughly 5 times more likely to be in the good 90-day clinical outcome group rather than poor outcome group if they presented with high cCBF at baseline imaging (OR 4.6, 95% CI 1.4-14.7,  $p=0.011$ ), while controlling for other significant contributing factors ( $p<0.05$ ): baseline NIHSS ( $p=0.015$ ) and DWI lesion volume ( $p=0.014$ ) (Table 2). Patients with good outcome had lower baseline NIHSS and smaller DWI lesion size compared to those with poor outcome. All patients with a DWI lesion volume  $\geq 66$  ml ( $n=18$ , 23%) had poor 90-day outcome. Representative cases are shown in Figure 3.

## Discussion

In this study, we demonstrated that higher CBF in the contralateral hemisphere is a strong determinant of good 90-day clinical outcome. This quantitative parameter, cCBF, varied strongly among patients, showing that there are marked inter-individual differences in CBF in the unaffected brain during acute ischemic stroke.

To quantify perfusion in acute stroke patients, MR- or CT-based bolus perfusion imaging is most commonly used, with a ratio between the affected and unaffected regions being a commonly reported metric.<sup>1, 12-15</sup> For example, the recent DEFUSE-3 trial used a cutoff of 30% of CBF based on the unaffected regions as a measure of irreversibly infarcted tissue using CTP.<sup>1</sup> However, this semi-quantitative approach neglects the fact that the CBF levels in non-affected regions may differ substantially between patients. Fully quantitative approaches may provide more information;<sup>5</sup> for example, Harston et al. have reported absolute CBF values in the acute stroke setting when evaluating serial perfusion imaging and tissue fate prediction.<sup>16</sup> Our results show, first, that there is a wide range of CBF in the contralateral hemisphere of stroke patients, which is in line with recent reports on patient-level mean cCBF.<sup>16</sup> This is not entirely unexpected as it is well-known that baseline CBF varies widely in patients of similar age, even though the explicit reasons for these variations are poorly understood.<sup>17</sup> When assessing patients using relative measures, this important information is lost, which could give insight into the patient's cardiac output or ability of the brain to deliver collateral flow. Other alternatives for quantitative perfusion measurements are H<sub>2</sub><sup>15</sup>O water PET and xenon CT;<sup>18, 19</sup> however, these approaches are difficult to implement in the acute settings, require radiation, and have high cost and personnel needs. ASL MRI is becoming increasingly available and has already been applied in the acute stroke setting in several

prior studies.<sup>7, 14, 16, 20</sup> While acquiring MRI in the acute stroke setting is often challenging, the WAKE-UP study showed that patients with unknown stroke onset profit from MRI and suggested general feasibility of MRI in an acute setting.<sup>21, 22</sup> There are a few studies that propose CT and MR bolus perfusion can be used in a quantitative manner to measure CBF;<sup>23-25</sup> however, this is still uncommon in clinical routine and has not been validated to the degree that ASL has. A comparison of ASL-cCBF with other imaging techniques related to blood flow, such as multiphase CT, would be valuable.

Recently, Raza and Rangaraju reviewed different existing prognostic scores to evaluate acute ischemic stroke clinically before endovascular treatment.<sup>26</sup> Looking at 10 different prognostic scores in acute ischemic stroke, the authors found a ceiling effect for the scores' area under the curve (AUC) with a prognostic accuracy of 0.8.<sup>26</sup> Only three scores included radiographic parameters additionally to traditional clinical information, either based on CT ASPECTS regional infarct lesion core (PRE score<sup>27</sup>, HIAT2 score<sup>28</sup>) or MRI DWI lesion core volume (SAD score<sup>29</sup>). After the introduction of the mismatch concept for MRI<sup>30</sup> and its translation to CT<sup>13, 31</sup>, there are several reports on other promising imaging parameters<sup>12, 32, 33</sup> and collaterals with good outcome.<sup>33-35</sup> While, however, predominately age, baseline NIHSS, CT ASPECTS, and MRI DWI lesion volume have been evaluated so far,<sup>27, 29, 36</sup> no such model includes quantitative CBF, largely due to the historical challenges of implementing such methods in the acute setting.

cCBF measurements could affect patient triage, therapy, and care at various different timepoints. High cCBF might represent a biomarker for underlying good overall health,<sup>37-39</sup> sufficient cardiac output,<sup>40, 41</sup> and/or capacity to provide good collateral flow.<sup>42, 43</sup> While we do not intend to alter any treatment recommendations with this observational study, our results may point at a future role

of cCBF as an objective and quantitative biomarker for therapy stratification: Dichotomized cCBF could be utilized as treatment decision tool supporting clinicians in deciding which patients might be suitable for IAT. One possibility is that patients with high cCBF on baseline MRI might be appropriate for more aggressive treatment.

Based on this study, we cannot assess the precise mechanism of why higher cCBF is associated with better outcomes; the size of the strokes and the baseline NIHSS scores were similar between the high and low cCBF groups. Potential causes of inter-individual baseline CBF levels are age, sex, end-tidal CO<sub>2</sub> level, cerebral diaschisis, and white matter (WM) lesion burden due to small vessel disease.<sup>44-49</sup> Older patients generally tend to show lower brain perfusion.<sup>37, 50-52</sup> Younger women tend to have higher brain perfusion compared to postmenopausal women and men, possibly due to differences in hematocrit.<sup>44, 53</sup> Another potential cause of higher cCBF could be higher arterial CO<sub>2</sub> levels, as could occur in patients with concomitant lung disease.<sup>46</sup> Unfortunately, we do not have information on CO<sub>2</sub> levels for our patients. However, if CO<sub>2</sub> levels were increased in sicker patients due to lung disease, this would be unexpected to improve their prognosis, as was seen with higher cCBF.

cCBF could also be affected by the presence of transhemispheric diaschisis, in which reduced afferent input to the contralateral hemisphere leads to depressed cCBF.<sup>54-56</sup> A xenon CT study in acute stroke patients found that cCBF was about 35% lower than in age-matched normal subjects.<sup>47</sup> One argument against diaschisis as a cause of reduced cCBF in our cohort is the lack of relationship of DWI lesion size with cCBF, although it is still possible that it could reflect a broader network-based effect.

Lower cCBF could also be related to small vessel ischemic disease (leukoaraiosis).<sup>48, 49, 57</sup> Prior stroke studies have shown that a high burden of white matter lesions is an indicator for bad neurological outcome.<sup>58, 59</sup> Small vessel disease leads to vascular dysfunction which then could result in CBF decrease and neuronal dysfunction. Our acute MR imaging protocol did not include fluid-attenuated inversion recovery (FLAIR) imaging, so we could not evaluate directly the role of leukoaraiosis on cCBF levels.

There are several limitations to this study. First, the sample size is limited and 17% of otherwise eligible patients were excluded from the study, primarily due to patient motion which is common in the acute stroke setting. Second, because of the prospective enrollment of patients in the iCAS study, studies were performed at different field strengths with slightly different ASL sequences (single vs. multi-delay), though this likely increases generalizability of the results. There were no differences in the percentage of patients in each group with single- and multi-delay ASL, nor was there any difference in the mean values of CBF based on the ASL type. Third, patients received different types of treatment (none/tPA/IAT/both). The study's regression model included information on reperfusion for the 53% of patients who received an IAT after the initial MRI exam. While cCBF is available for all patients, this study cannot assess the extent of reperfusion and collateral circulation of patients who received no or only tPA treatment. Fourth, as expected, the acute DWI lesion volume at baseline had a large impact on outcome, though we found a strong effect of cCBF even when this was controlled for in our analysis. Fifth, we note that use of cCBF is not applicable in bilateral stroke because there is no unaffected hemisphere. Even the presence of large non-acute contralateral infarcts could confound the interpretation of cCBF, though excluding them from the analysis would be straightforward. Sixth, there was no systematic information recorded on the contralateral arterial vessel status at the cervical level; intracranial

MRA was available in 75/77 subjects and only 1 patient in the low cCBF group (cCBF 36.7 ml/100 g/min) had a significant stenosis or occlusion (ICA occlusion). But since the cervical region was not imaged, we cannot determine whether stenosis or occlusion at the carotid bifurcation was associated with low cCBF.



## **Conclusion**

Quantitative contralateral CBF is a significant predictor of clinical outcome at 90 days. High cCBF predicts good outcome, even when controlled for baseline NIHSS, DWI lesion size, and intra-arterial treatment. Quantitative CBF is a predictive measurement that may be valuable for acute stroke triage, treatment, and general outcome prognosis.

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## **Disclosures**

Thoralf Thamm received an academic scholarship from the German Academic Scholarship Foundation (Studienstiftung des deutschen Volkes) during the conduct of the study. Dr Marks owns stock in ThrombX Medical Inc. Dr Christensen has an equity interest in iSchemaView. Dr Do is a consultant for Microvention. Dr Jovin received a research grant from Stryker Neurovascular as PI of the AURORA trial; is an investor/advisor for Anaconda, FreeOx Biotech, Corindus, and Route92; owns stock in VizAi and Blockade Medical; and is a consultant for Cerenovus. Dr Lansberg is a consultant for Novo Nordisk, Genentech, Biogen and Moleac. Dr Albers is a consultant for and has an equity interest in iSchemaView; he also reports a patent for an automated AIF. Dr Zaharchuk received funding support from GE Healthcare and Bayer Healthcare; and has an equity interest in Subtle Medical. The other authors report no conflicts.

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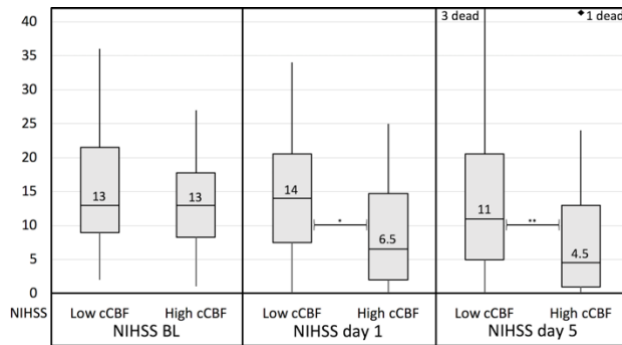
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## Figures and Figure Legends

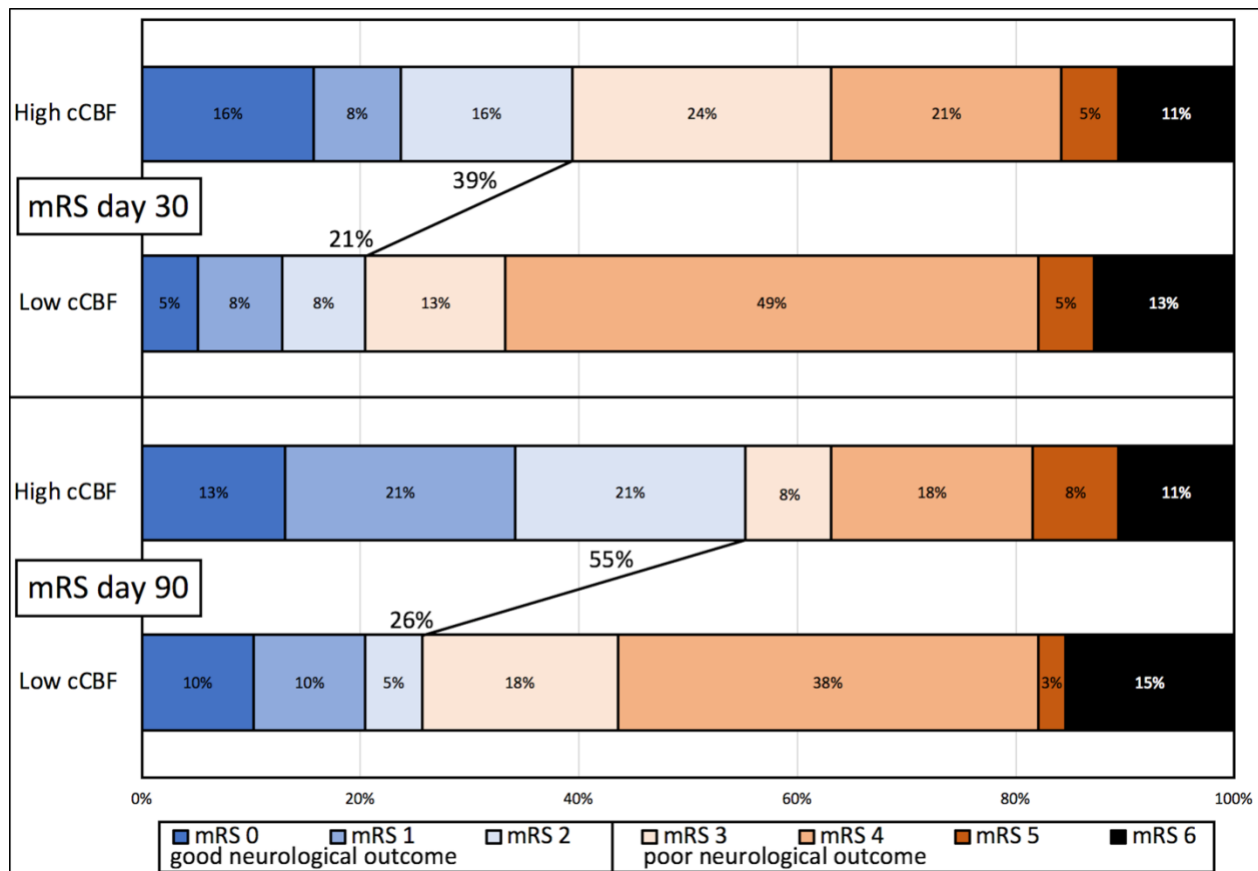
**Figure 1.** Boxplot diagram depicting NIHSS at baseline (BL), day 1, and day 5 for low and high cCBF groups.



### Legend:

While there were no differences for NIHSS at baseline ( $p=0.28$ ), the differences were significant between groups at day 1 ( $*p=0.016$ ) and day 5 ( $**p=0.003$ ). cCBF indicates contralateral cerebral blood flow; and NIHSS, National Institutes of Health Stroke Scale.

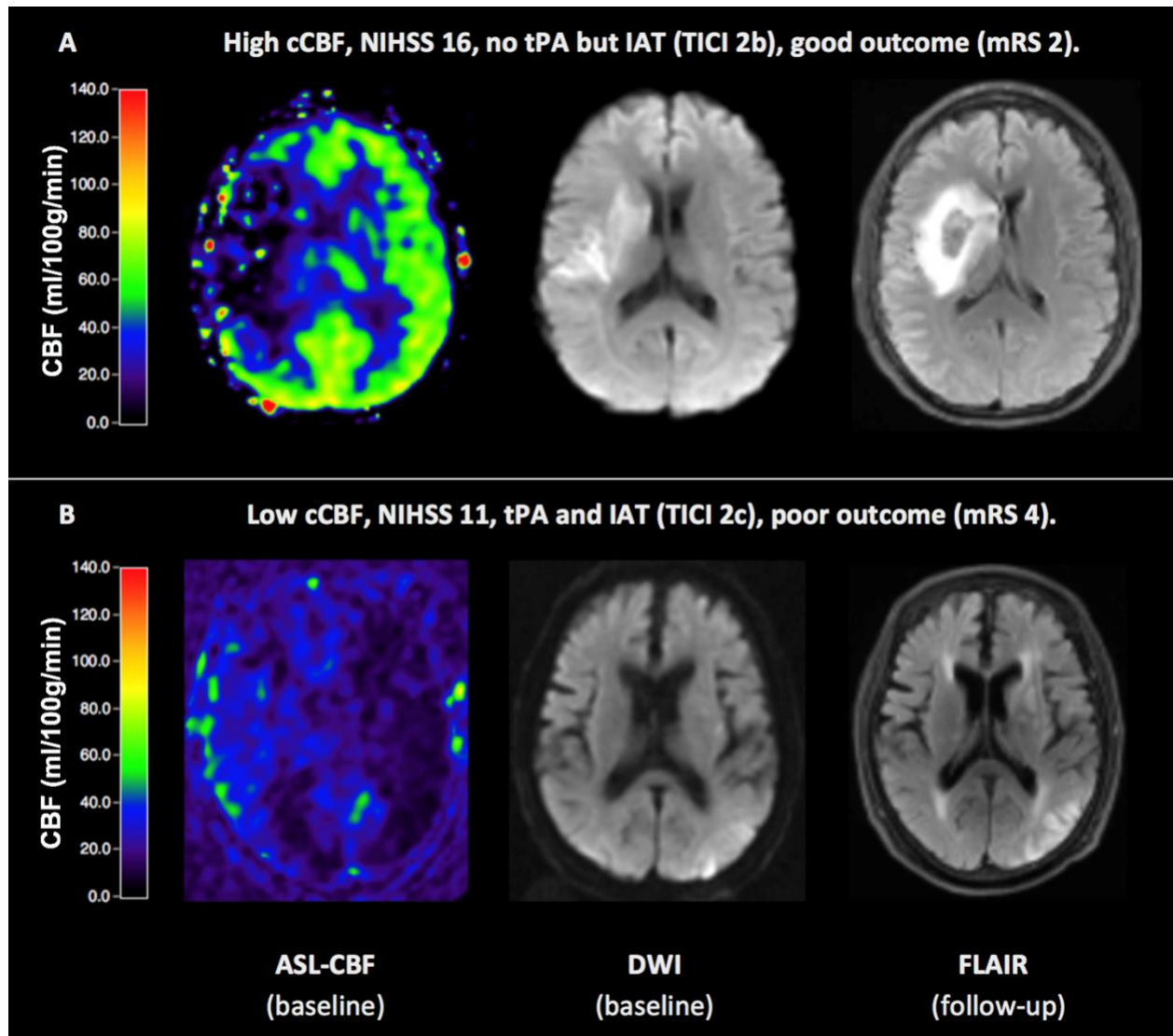
**Figure 2.** mRS outcome at day 30 and 90 stratified by dichotomized cCBF (low vs. high cCBF group).



**Legend:**

Patients with high cCBF were significantly more likely to have a good outcome at day 90 (Fisher's exact test,  $p=0.011$ ). There was a trend towards similar good outcomes at day 30, but this did not reach statistical significance ( $p=0.09$ ). cCBF indicates contralateral cerebral blood flow; and mRS, modified Rankin Score.

**Figure 3.** Representative patient cases.



**Legend:**

**A:** 46 year-old female. Left-sided hemiplegia, partial facial drop with total gaze paralysis, moderate sensory loss, complete hemianopia, and profound hemi-neglect. Baseline NIHSS of 16, DWI lesion 37 mL, cCBF 58.1 ml/100g/min. No tPA but IAT with successful reperfusion (TICI 2b). Day 90 mRS = 2. **B:** 66 year-old male. Severe aphasia, partial facial paralysis, and bilateral hemianopia. Baseline NIHSS of 11, DWI lesion 0 ml, cCBF 28.3 ml/100g/min. Both, tPA and IAT with successful reperfusion (TICI 2c). Day 90 mRS = 4. CBF indicates cerebral blood flow; cCBF,

contralateral CBF; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; IAT, intra-arterial therapy; TICI, thrombolysis in cerebral infarction; mRS, modified Rankin Score; ASL, arterial spin labeling; DWI, diffusion-weighted imaging; and FLAIR, fluid-attenuated inversion recovery.

**Table 1.** Demographics and baseline imaging information.

<b>Variable</b>	<b>Full cohort (n=77)</b>	<b>High cCBF group (n=38)</b>	<b>Low cCBF group (n=39)</b>	<b>p; High vs. low cCBF</b>
Age, median (IQR), years	66 (55-76)	63 (56-78)	66 (54-76)	0.98
Sex, female, No. (%)	41 (53)	23 (61)	18 (46)	0.26
Onset-to-imaging time (OIT), median (IQR), hrs	4.8 (3.6-7.7)	4.7 (3.2-7.7)	5.0 (4.3-7.0)	0.62
DWI lesion volume, median (IQR), ml	16.7 (6.1-51.2)	17.8 (6.4-49.7)	15.2 (5.4-67.9)	0.84
NIHSS baseline, median (IQR)	13 (9-20)	13 (8-18)	13 (9-22)	0.28
cCBF, median (IQR), ml/100g/min	38.9 (31.2-44.5)	44.6 (41.6-50.8)	31.2 (28.0-35.0)	<0.001*
tPA therapy, No.(%)	46 (60)	20 (53)	26 (67)	0.25
Intra-arterial therapy (IAT), No. (%)	41 (53)	21 (64)	20 (51)	0.82
TICI 2b-3 among all IAT, (%)	33/41 (80)	15/21 (71)	18/20 (90)	0.24

\* Statistically significant,  $p < 0.05$

cCBF indicates contralateral cerebral blood flow; IQR, interquartile range; DWI, diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; and TICI, thrombolysis in cerebral infarction.

**Table 2.** Univariate and multivariable analyses (logistic regression) for good outcome (mRS 0-2) using dichotomized cCBF groups while controlling for potential confounders. In the adjusted multivariable model, DWI lesion volume and baseline NIHSS were identified as significant contributing factors.

Variable	Univariate analysis (unadjusted)			Multivariable analysis (adjusted) <sup>†</sup>		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Age	0.98	0.95 - 1.02	0.31	---	---	---
Sex	0.72	0.30 - 1.85	0.52	---	---	---
Previous stroke	0.38	0.07 – 2.01	0.26	---	---	---
Onset-to-imaging-time (OIT)	0.96	0.82 - 1.12	0.61	---	---	---
NIHSS at baseline	0.86	0.80 - 0.92	<0.001*	0.89	0.81 - 0.98	0.015*
DWI lesion volume	0.97	0.95 - 0.99	<0.001*	0.98	0.96 - 1.00	0.014*
tPA therapy	1.11	0.44 – 2.84	0.82	---	---	---
Intra-arterial therapy (IAT)	2.73	1.05 - 7.12	0.04*	1.59	0.49 – 5.13	0.44
TICI 2b - 3	2.00	0.40 – 9.97	0.40	---	---	---
High cCBF (≥39ml/100g/min)	3.58	1.36 - 9.43	0.010*	4.56	1.41 - 14.73	0.011*

\* Statistically significant,  $p < 0.05$

<sup>†</sup> Multivariable logistic regression model for high cCBF, adjusting for potential confounders (NIHSS at baseline, DWI lesion volume, and intra-arterial therapy)

mRS indicates modified Rankin Score; NIHSS, National Institutes of Health Stroke Scale; DWI, diffusion-weighted imaging; tPA, tissue plasminogen activator; TICI, thrombolysis in cerebral infarction; and cCBF, contralateral cerebral blood flow.